REMARKS

Claims 1-34 were previously pending in this application. By this amendment, Applicant has canceled claims 5, 6, 8, 9, 12, 13, 16-23, 26 and 27 without prejudice or disclaimer. Claims 7, 14, 15, 24, 25, 28, 29, 33 and 34 have been amended. As a result claims 1-4, 7, 10, 11, 14, 15, 24, 25 and 28-34 are pending for examination.

Claim Objections

The Examiner objected to claim 25 because sequence identifiers were not used in the claim. Applicant has amended the claim to insert sequence identifiers. Accordingly, Applicant respectfully requests that the objection to claim 25 be withdrawn.

Rejections Under 35 U.S.C. § 112

The Examiner rejected claims 1-21 and 24-34 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner indicated that there was a lack of an adequate written description because the specification does not disclose polynucleotide sequences encoding a DXPS protein. Applicant respectfully traverses the rejection.

The specification teaches peptide sequences of DXPS from three different bacterial organisms, showing in a schematic manner the common structural elements of the peptide sequences (see Figure 3 and SEQ ID NOs:1-3). Contrary to the Examiner's opinion that the Applicant fails to describe structural features common to members of the claimed genera of polypeptides, the specification teaches that all three polypeptides illustrated in Figure 3 share common conserved domains characteristic for the DXPS protein (page 21, lines 2 to 13).

Furthermore, the cloning and characterization of DXPS from a number of organisms is well known in the art and the specification includes references to scientific publications and also Genbank accession numbers (for example, see page 2, lines 17 to 27, description of Figure 3, page 13, lines 33 to page 14, line 15 and example 1, page 16, lines 15 to 29).

Accordingly, the subject matter of the claims is described in such a way in the description as to convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed.

Regarding the Examiner's contention that Applicant did not provide a written description of the claimed nucleic acid sequences, the Examiner's attention is drawn to the relevant section of the MPEP, which contains the following discussion of this subject matter:

> Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. For example, in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species."
>
> MPEP § 2163.II.A.3.a.ii. (8th ed., rev. 2 2004).

Moreover, the law recognizes that the disclosure of an amino acid sequence serves as an adequate written description of the genus of nucleic acid molecules that encode the amino acid sequence. Cf. In re Deuel, 51 F.3d 1552 (Fed. Cir. 1995); In re Bell, 9991 F.2d 781, 785 (Fed. Cir. 1993).

Accordingly, withdrawal of the rejection of claims 1-21 and 24-34 under 35 U.S.C. 112, first paragraph, is respectfully requested.

The Examiner also rejected claims 1-21 and 24-34 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method of overexpression of DXPS in *E. coli* and increased lycopene and Co8 production, does not reasonably provide enablement for manipulating or increasing isoprenoid production in plants or other cells or organisms, other than

E. coli, transformed with DXP synthase or any other combination of polynucleotides encoding an isoprenoid producing protein.

The Examiner alleges that the invention is not enabled as it is directed to any DXPS in any organism, but only overexpression of *E. coli* DXPS in *E. coli* and tomato transformed with *E. coli* DXPS as shown.

First, Applicant notes that claims 14 and 24 have been amended and accordingly, the invention relates to expression of DXPS in plants, yeast or algae, not any organism.

Second, Applicant was the first to show that expression of DXPS leads to increased IPP activity. The specification illustrates the invention using tomato plants and *E. coli* DXPS. However, the specification teaches that a host cell of any plant variety may be used (page 12, line 35 to page 13, line 14). The example showing the transformation of tomato plants merely illustrates the invention and does not limit the invention to plants of the *Lycopersicon spp.*

The mevalonate independent pathway for IPP formation has been identified in eubacteria, green alga and in plastids of higher plants. It is well known in the art that plastids are of prokaryotic origin and are therefore highly conserved amongst different plants. Accordingly, a person skilled in the art would predict and expect that the mevalonate independent pathway for IPP formation is conserved in higher plants. Therefore, one skilled in the art would also have a reasonable expectation that the overexpression of DXPS in plants other than plants of the *Lycopersicon spp.* would lead to increased IPP activity. Even if the person of skill were to carry out some experimentation in order to establish that overexpression of DXPS in a certain plant species does in fact increase IPP activity, this type of experimentation is entirely routine within the art. Accordingly, no undue experimentation involving the testing of other plant species is required.

Furthermore, a skilled person would also understand that if the expression of *E. coli* DXPS in plants leads to an increase in IPP as shown by Applicant, then the same result could be achieved with DXPS from other bacteria because DXPS from different kingdoms are highly

conserved. Furthermore, a skilled person would understand that the result could be achieved by overexpression of endogenous plant DXPS from one plant in a different plant due to the high conservation of the mevalonate independent IPP pathway. In fact, Burkhardt (The Plant Journal, 1997, 105(5):1071-1078, cited by the Examiner) shows that expression of a plant enzyme from one plant in a another plant from a different family can successfully affect a biochemical pathway.

The Examiner also alleges that the state of art for isolating DNAs of defined function is highly unpredictable. Applicant respectfully disagrees with the Examiner on this matter. The sequence of a number of DXPS polynucleotides is known in the art as discussed above. It is a routine matter in the field of molecular biology to isolate homologous sequences from different organisms using a known sequence from a specific organism. In particular, in the event that it is known that the peptides are highly conserved and share a number of conserved motifs, it is a matter of routine skill to isolate homologous sequences and further characterize them by PCR and sequencing techniques, all of which are well known to and routinely practiced by the person of ordinary skill in the art. This is acknowledged by the Examiner on page 7 of the Office Action (last paragraph).

The Examiner's suggestion on page 7 of the Office Action that one of ordinary skill in the art would have to "make and clone a multitude of non-exemplified DXP synthase and isoprenoid producing nucleic acid sequences" and to perform testing in a "myriad of non-exemplified plants or bacteria" is an overstatement of what the person of ordinary skill in the art would be required to do. In addition to ignoring the advanced level of skill in the art of plant molecular biology, which already provides a number of gene sequences relevant to the claimed invention, and the routine nature of the experimentation (as addressed above), the Examiner's statement does not consider the conservation of this biosynthetic pathways in any meaningful way. Given the conservation of plastids and the DXPS gene sequences of interest, as well as the products of the biosynthetic pathways in plants, one of ordinary skill in the art would not be required to undertake anything other than routine experimentation in order to carry out the claimed invention. Exercise of routine experimentation to practice the invention is not sufficient for an enablement rejection. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.

1988) (citing In re Angstadt, 537 F.2d 489, 502-504, 190 USPQ 214, 217-219 (CCPA 1976)) (a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance). See also Ajinomoto Co. v. Archer-Daniels Midland Co., 228 F. 3d 1338, 1345 (Fed. Cir. 2000) (no undue experimentation where conventional and well-known genetic engineering techniques used).

Thus the teaching of the specification in combination with the high level of skill in the art and the knowledge of the person of ordinary skill (as evidenced by the references cited by the Examiner) favor a conclusion that the claimed invention is enabled throughout its scope.

The Examiner also alleges that the invention is not enabled because it relates to non-exemplified isoprenoids and refers to a publication by Shewmaker (The Plant Journal, 1999, 20(4): 401-412). However, this reference in fact teaches an overall increase of isoprenoids by expression of phytoene synthase (PS). The invention relates to manipulating the isoprenoid pathway and to an increased activity of isoprenoids. The first step in the mevalonate independent pathway is a rate limiting step, as the Applicants have shown for the first time. Once in possession of this information, a person skilled in the art would predict that manipulation of this first step increases the overall content of isoprenoids. It is also reasonable to expect that the levels of all isoprenoids compounds will be increased.

Shewmaker on the other hand discloses the manipulation of a step which is a downstream step in isoprenoid synthesis and relates to the conversion of GGPP to phytoene. Whilst the overall content of IPP and in particular the content of carotenoids increases, the content of other IPP compounds decreases. However, it seems that the manipulation of a downstream reaction step interferes with other interaction steps. As the present invention concerns the first step of the reaction, Applicant does not agree that Shewmaker is relevant to demonstrate a lack of enablement.

Therefore, Applicant asserts that there is no undue experimentation required to practice the invention, as the application combined with the state of art presents enough guidance to a person skilled in the art to carry out the invention.

Accordingly, withdrawal of the rejection under 35 U.S.C. 112, first paragraph, for lack of enablement, is respectfully requested.

Claims 20-21 and 25-26 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant has canceled claims 20, 21 and 26, making the rejections of those claims moot. Applicant has amended claim 25 to recite nucleotide sequences that encode specific polypeptide sequences (SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3).

Accordingly, withdrawal of the rejection under 35 U.S.C. 112, second paragraph, is respectfully requested.

Rejections Under 35 U.S.C. § 101

The Examiner rejected claims 29, 33 and 34 under 35 U.S.C. § 101 because the claimed invention is the claimed inventions encompass untransformed plants and seeds, which are a product of nature and not one of the five classes of patentable subject matter. The Examiner indicated that claims 29, 33 and 34 are drawn to progeny and parts such as seeds and fruits of a transformed plant.

The Examiner alleges that the subject matter of claims 29, 33 and 34 comprises untransformed plants and seeds. The claims have been amended in response to the Examiner's objection, thereby obviating the rejection.

It is submitted that a skilled person will understand that the plants or plant parts identified in the highlighted claims relate to plants or parts thereof comprising the transgene as they are characterized by having increased isoprenoid activity. In view of the amendments described

above, the subject matter of the claims relates not only to a distinguishing phenotype but also a distinguishing genotype, i.e., the presence of a transgene.

Accordingly, the subject matter of the claims fulfils the requirements of 35 U.S.C. 101, and Applicant respectfully requests that the Examiner withdraw the rejection.

Rejections Under 35 U.S.C. § 102

The Examiner rejected claims 24-25 and 29 under 35 U.S.C. § 102(b) as being anticipated by Lange *et al.*, PNAS March 3, 1998; Vol. 95, No. 5; pages 2100-2104. Applicant respectfully traverses the rejection.

Lange *et al.* teaches the cloning of a DXP synthase (DXPS) from peppermint which was used to transform *E. coli*. Induction with IPTG showed that bacteria carrying the transgene had enhanced DXPS activity. In response to the Examiner's objection, the limitation of claim 27 has been included in claim 24, which now relates to plants only. Lange *et al.* does not disclose a transgenic plant having a mevalonate independent IPP biosynthetic pathway and increased isoprenoid activity which comprises at least one transgene capable of expressing DXPS or a functional equivalent thereof. Applicant is the first to show that the first reaction in the mevalonate independent pathway catalyzed by DXPS is a rate limiting step and the first to generate transgenic plants comprising a DXPS transgene.

Lange *et al.* does not disclose all of the limitations of the invention as now claimed. Accordingly, withdrawal of the rejection under 35 U.S.C. 102 is respectfully requested.

Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 1-15, 18, 21, 24-27 and 29-31 under 35 U.S.C. § 103(a) as being unpatentable over Burkhardt *et al.*, The Plant Journal, 1997, 105(5):1071-1078, in view of Lange *et al.* PNAS 1998, 95(5):2100-2104. Applicant respectfully traverses the rejection of the

claims as now amended. The amended set of claims relates to plants and also to algae and yeast (e.g., claim 14).

Burkhardt reference

Burkhardt discloses the transformation of rice plants with a daffodil phytoene synthase (PS). PS is involved in the biosynthetic pathway of carotenoids and uses geranyl geranyl diphosphate as a substrate. Burkhardt discloses that overexpression of daffodil PS induces carotenoid production in rice. Burkhardt teaches nothing of modifying plants to express DXPS.

PS is an enzyme that acts in the biochemical synthesis of carotenoids, which is only one of many groups of isoprenoids. Other isoprenoids such as gibberellins and sterols are synthesized using different branches of the isoprenoid pathway. Accordingly, PS is specifically involved in one downstream step of the synthesis of IPP, namely the conversion of geranyl geranyl diphosphate to a C_{40} tetraterpene for the synthesis of carotenoids.

There is no mention whatsoever in the Burkhardt reference of DXPS and mevalonate independent pathways of isoprenoid production. Burkhardt does not disclose that the first reaction in the mevalonate independent pathways is a rate limiting step. Moreover, there is no indication that enzymes involved in the isoprenoid pathway other than PS can be overexpressed and that this would lead to an increase in isoprenoids.

Lange reference

The Examiner alleges that a person skilled in the art would have been motivated by Lange to modify the teaching in Burkhardt. Lange teaches that the expression of a DXPS derived from peppermint leaves in bacteria increases DXPS activity. Lange does not teach that the first reaction in the mevalonate independent pathway catalyzed by DXPS is a rate limiting step. Therefore, there is no indication in Lange that the conversion catalyzed by DXPS is in fact of great importance in the IPP biosynthetic pathway.

There is no suggestion in Lange that the expression of DXPS in plants, yeast or algae would alter isoprenoid expression and in fact, there is no suggestion in Lange that expression of DXPS in an organisms other than *E. coli* is possible.

The Combination of References is Insufficient for Obviousness

Although Lange shows that the expression of a plant DXPS in bacteria stimulates DXPS activity, a skilled person would not use this teaching together with the disclosure in Burkhardt in a method for transforming plants with DXPS (claims 1 to 9) or making a plant cell transgenic for DXPS (claims 10 to 13) because there is no indication in either document that DXPS can work in transgenic plants, algae or yeast as is presently claimed. Accordingly, there would be no motivation for a person skilled in the art to use the teaching of Lange to modify the teaching of Burkhardt in order to express DXPS in plants, algae or yeast.

Moreover, even if the person of skill in the art were motivated to express DXPS in plants, algae or yeast, which Applicant disputes, the skilled artisan would not have a reasonable expectation of success at the time of filing of the instant application based on the teachings of Burkhardt and Lange. Due to the complexity of the biochemical pathway of IPP, it is not reasonable for a person skilled in the art to expect that because the overexpression of a plant PS in rice increases carotenoid content, the overexpression of any enzyme involved in isoprenoid production would lead to an increase of isoprenoids. The observation that other enzymes can be transgenically expressed in plants, even if they are also involved in the isoprenoid pathway, does not allow the conclusion that (over)expression of any enzymes could work, even if it has been successfully expressed in bacteria.

In fact, the Examiner appears to concur, having stated in the Office Action that "the phenotypic character expected from expression of a DNA construct often cannot be reliably predicted." Office Action at 7. In view of this unpredictability postulated by the Examiner, a skilled person would not seek or reasonably expect to modify the IPP content in plants, algae or yeast by expression of DXPS.

Applicant, however, has surprisingly found that the first reaction in the mevalonate independent pathway catalyzed by DXPS is a rate limiting step and that expression of DXPS or a functional equivalent thereof in plants can lead to an increase in IPP. Thus, without Applicant's teaching one of ordinary skill in the art would not have had a reasonable expectation of success in carrying out the claimed invention.

Accordingly, in view of the foregoing, withdrawal of the rejection under 35 U.S.C. 103 is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
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